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EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,859	DANIELS ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claim 8 is objected to because of the following informalities: there appears to be a misspelling in the item "hydroxyprophylmethylcellulose" in line 6. Appropriate correction is required.

Comments and Notes

2. It is noted that in some claims the various components are referred to by roman numerals whereas in other claims, these same components are referred to by the functional description which follows the roman numerals. It is respectfully suggested that for consistency, only one of these reference schemes be used throughout the claims.

Claim Rejections - 35 USC § 112 – 1st Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. None of the semisynthetic cellulose derivatives other than those explicitly recited in the application meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus of semisynthetic cellulose derivatives encompassed by the claim, since there is no description of the structural relationship of these derivatives provided in the specification and Applicant has not provided a description as to how the base molecule may be changed while remaining a derivative and being only semisynthetic.

Components (ii), (iii), (iv) and (v) also fail to fully comply with the written description provision. These components are each defined using functional language and some examples of factors or agents suitable for each of these components are given in the specification. These definitions do not include only art recognized classes of ingredients (e.g., amino acids) but rather by the effect of a particular ingredient (e.g. factor or agent that promotes cell attachment). While the person of ordinary skill in the art could determine whether a particular compound meets the functional limitation of the instant claims that is insufficient to meet this provision. A description which renders the

claim invention obvious does not satisfy the written description requirement (*Ariad v. Eli Lilly*, 598 F3d 1336, 94 USPQ2d 1161, citing *Lockwood v. Am. Airlines*).

5. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising agents suitable for use in the treatment of an ocular surface disease, disorder or damage and the prophylaxis of ocular surface diseases and disorders, does not reasonably provide enablement for compositions comprising agents the prophylaxis (prevention) of ocular surface damage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure and claims of the application have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation

The factors include:

1. The nature of the invention;
2. The breadth of the claims;
3. The predictability or unpredictability of the art;
4. The amount of direction or guidance presented;
5. The presence or absence of working examples
6. The quantity of experimentation necessary;
7. The state of the prior art; and

8. The relative skill of those skilled in the art.

Each relevant factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1. The nature of the invention, breadth of the claims: compositions comprising a carrier; a factor or agent that promotes the health of the ocular surface (component (ii)) and an agent capable of establishing or maintaining a stable tear film by altering fluid properties (component (iii)) with claim 2 requiring an additional ingredient (iv) of one or more agents for use in the treatment or prophylaxis of an ocular surface disease, disorder or damage. Exemplified compounds for component (iv) set forth in the specification (¶ [0093] of the PGPub of the instant specification) include secretory antibodies, anti-inflammatory agents and inhibitors of angiogenesis and proteases.

2. The amount of direction or guidance presented, the presence or absence of working examples and the relative skill of those skilled in the art: various formulations are prepared and there appears to be little unpredictability in the ability to prepare these formulations. The relative skill of those skilled in the art is high. Ocular damage includes surgical incisions, trauma and other unpredictable events (e.g., cuts or abrasions to the ocular surface). There are no examples given of how the use of the claimed compositions will be able to prevent such damage from occurring although the

compositions could be useful in the treatment of such damage after it occurs. Safety glasses could prevent unexpected trauma or damage but the preparations do not contain any ingredients that would form a protective covering over the eye that would prevent such damage from occurring. The compositions are capable of treating such damage once it occurs but not preventing the damage from occurring in the first place.

Since the term "treatment" is inclusive of various administrative timing schemes and thus provides adequate coverage for all reasonably successful therapies, the examiner recommends deleting the term "prophylaxis" and simply reciting "treatment" instead.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1 – 17, 20 and 22 – 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 defines components (ii) and (iii) and component (v) of claim 3 are all required to be "synthetic or recombinant or licensed for pharmaceutical use". It is unclear what factors and agents meet these limitations. Does Applicant mean 'licensed' in the sense of patent rights that have been licensed to another party? Or does "licensed for pharmaceutical use" mean that the

factors and agents have been approved, either presently or at one time, by one or more of the various regulatory agencies throughout the world? Please clarify.

8. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what items are within the Markush group of claim 8. Hypromellose is another name for the semisynthetic cellulose derivative hydroxypropylmethyl cellulose (HPMC), which also appears to be present in the same Markush group, although with an apparent typographical error. Did Applicant intend for these to be different cellulose compounds instead of repeating the same element under two different names? It is unclear if applicant does not consider hypromellose/HPMC to be a semisynthetic cellulose derivative due the listing of this compound separately. Please clarify.

9. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The units of osmolarity are moles of solute per liter of solvent, and as such, typically has units of osmoles (Osm or Osmol) per liter of solvent. The units for the values in claim 14 do not have the 'per kilogram of solvent' portion in the units. It is unclear if Applicant is claiming particular number of moles of solute in some unspecified volume and not osmolarity or if the wrong units have. Please clarify.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 5 – 7, 12, 17, 20 and 22 – 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Tiffany et al. (US 6,565,861).

Tiffany et al. discloses formulations suitable for application to mammalian eyes which contain a lipid biding protein and a polar lipid present as a soluble complex in an aqueous electrolyte (abstract). The lipid binding protein can be tear lipocalin (col 2, ln 25), which is identified by Applicant as an agent capable of establishing or maintaining a stable tear film and a component of meibomian gland secretions (¶ [0090] of the PGPub of the instant application), reading on component (iii) of claim 1. The polar lipids also read on component (iii) (instant application, ¶ [0090]). The bulk ions in the water read on component (ii) and (i) of claim 1 respectively. The drops can be delivered in a single dose ampoule (col 3, ln 13 – 15). The formulations provides a substitute for natural tears that will also be useful in the treatment of eye irritations (col 3, ln 23 – 30), which reads on the treatment of dry eye and inflammation of the eye.

In regards to the limitation of claim 1, “synthetic” and “recombinant" are being treated as limitations on the manner in which the particular factor or agent was produced. There is no evidence that the lipids and proteins used by Tiffany et al. are

structurally different from those synthesized or generated recombinantly in the laboratory (e.g., the polar lipids have the same structure whether they are isolated from cell membranes or synthesized *de novo* in the laboratory). Therefore, this limitation is met by Tiffany et al.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 2, 4 – 15, 17, 20 and 22 – 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tiffany et al. (US 6,565,861).

Tiffany et al. discloses formulations suitable for application to mammalian eyes which contain a lipid biding protein and a polar lipid present as a soluble complex in an aqueous electrolyte (abstract). The lipid binding protein can be tear lipocalin (col 2, ln 25), which is identified by Applicant as an agent capable of establishing or maintaining a stable tear film and a component of meibomian gland secretions (¶ [0090] of the PGPub of the instant application), reading on component (iii) of claim 1. Other preferred protein choices include lysozyme, lactoferrin or IgA (col 2, ln 48 – 49), which are anti-microbial agents (¶ [0093] of the instant application). The polar lipids also read on component (iii) (instant application, ¶ [0090]). The bulk ions in the water read on component (ii) and (i) of claim 1 respectively. The aqueous electrolyte should be buffered at a pH of 5 – 8.5 (col 2, ln 24 – 35). The formulation can also contain the mucolytic agent N-acetylcysteine, which reads on the Markush group of component (iv) set forth in instant claim 4. Key physical properties for the function of fluid tears are surface tension and viscosity (col 1, ln 43 – 46). Components such as hypromellose (HPMC), polyvinyl pyrrolidone (povidone), polyvinyl alcohol, dextran or hyaluronic acid can be included in artificial tears to improve the viscosity of the composition and to mimic the mucus

present on the corneal surface (col 1, ln 19 - 30). The formulations preferably show shear-thinning and/or a surface tension of less than 47 mN/m (47 dyne/cm; col 2, ln 36 – 39). The formulation is also preferably isotonic or slightly hypotonic with an osmotic pressure ranging between 200 - 500 mOsmol/kg (col 2, ln 44 - 47). While osmolality as reported in Tiffany and osmolarity as in the claims are slightly different properties (moles divided by either liters of solvent or moles of solvent), for diluent solutions the two quantities are quite similar). The drops can be delivered in a single dose ampoule (col 3, ln 13). Such compositions are preferably sterile, which renders unnecessary the inclusion of bacteriostatic components such as benzalkonium chloride in the formulation (col 3, ln 13 – 15; col 2, ln 31 - 34). The components of the invention can also be delivered to the eye in a concentrated gel or other vehicle (col 3, ln 19 – 22). The formulations provides a substitute for natural tears that will also be useful in the treatment of eye irritations (col 3, ln 23 – 30), which reads on the treatment of dry eye and inflammation of the eye. Better understanding of the properties of natural human tears will provide better formulations for the treatment or alleviation of dry eye symptoms (col 1, ln 37 – 39).

Tiffany et al. does not explicitly prepare single dose formulation without benzalkonium chloride or formulations that include component (iv).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to prepare formulation with a mucolytic agent such as N-acetylcysteine and/or agents such as hypromellose that alter the viscosity of the composition and also mimic the mucus present on the corneal surface. By preparing a

sterile single dose formulation, formulations that do not require bacteriostatic agents such as benzalkonium chloride can be readily prepared and administered without worries about microbial contamination. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Tiffany et al. discloses those embodiments can be prepared while not setting forth an exemplary formulation meeting the limitations. It also would be obvious to use the artificial tear formulations with properties of natural human tears to humans for the treatment of afflictions such as dry eye or inflammation of the eye as Tiffany et al. discloses that the formulations can be used in the treatment of such indications.

The range of disclosed values for the pH, surface tension and osmolality of the artificial tear formulation disclosed by Tiffany et al. overlap with the ranges recited in the instant claims and overlapping ranges are *prima facie* obvious. The pH, surface tension and tonicity of the composition are clearly result effective parameters that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the types of ingredients and amounts of those ingredients to add in order to best achieve the desired results of a product that replicates the various properties (e.g., surface tension and tonicity) of human tears when administered to a human eye.

In regards to the limitation of claim 1, “synthetic” and “recombinant" are being treated as limitations on the manner in which the particular factor or agent was

produced. There is no evidence that the lipids and proteins used by Tiffany et al. are structurally different from those synthesized or generated recombinantly in the laboratory (e.g., the polar lipids have the same structure whether they are isolated from cell membranes or synthesized *de novo* in the laboratory). Therefore, this limitation is met by Tiffany et al.

16. Claims 1 – 15, 17, 20 and 22 – 25 rejected under 35 U.S.C. 103(a) as being unpatentable over Tiffany et al. as applied to claims 1, 2, 4 – 15, 17, 20 and 22 – 25 above, and further in view of Belkin et al. (US 5,510,329).

As discussed in greater detail above, Tiffany et al. discloses artificial tear compositions comprising components (i) – (iii) and optionally (iv) that mimic various properties of human tears. The compositions can be used to treat various afflictions of the eye, such as dry eye.

Tiffany et al. does not disclose the inclusion of an ingredient (v) such as fibroblast growth factor (FGF).

Belkin et al. discloses an ophthalmological composition that induces regeneration of the corneal epithelium in humans that uses FGF as the active agent in a suitable buffer system (col 1, ln 66 – col 2, ln 1; col 2 ln 14 – 15). Advantageously also present in the formulation is an aqueous viscoelastic composition to provide the desired degree of viscosity and adherence to the formulation (col 2, ln 18 – 22) when administered to the eye.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate FGF into the artificial tears formulation of Tiffany et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Belkin et al. discloses that when applied to the eye in viscoelastic solution such as the artificial tear formulation of Tiffany et al., FGF will induce regeneration of corneal epithelium. The inclusion of this ingredient in the artificial tear formulation will aid in the repair of the eye after such damage occurs and provide a liquid that mimics the properties of natural human tears.

In regards to the limitation of claim 3 that component (v) be "synthetic, recombinant or licensed for pharmaceutical use, "synthetic" and "recombinant" are being treated as limitations on the manner in which the particular factor or agent was prepared. The FGF used in Tiffany is isolated from bovine brain (col 3, ln 33 onward) but there is no evidence that FGF isolated from a natural source is distinct from FGF that has been synthesized or recombinantly expressed. Therefore, this limitation is met by the isolated FGF used by Belkin et al.

17. Claims 1, 2, 4 – 17, 20 and 22 – 25 rejected under 35 U.S.C. 103(a) as being unpatentable over Tiffany et al. as applied to claims 1, 2, 4 – 15, 17, 20 and 22 – 25 above, and further in view of Hu et al. (US 6,037,328).

As discussed in greater detail above, Tiffany et al. discloses artificial tear compositions comprising components (i) – (iii) and optionally (iv) that mimic various

properties of human tears. The shear-thinning and surface tension of the compositions are important factors to match the physical properties of the artificial tears to the properties of natural human tears.

Tiffany et al. does not provide explicit values for the preferred viscosity of the artificial tear formulations.

Hu et al. discloses ophthalmic solution in the form of drops which are applied to the eye to rewet or lubricate contact lens (col 3, ln 20 – 25). Viscosity builders are present in the formulation to provide a viscosity of between 1 and 50 cps, preferably at least 2 cps (col 5, ln 43 – 47).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to prepare an artificial tear formulation as taught by Tiffany et al. with a viscosity of between 1 and 50 cps. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Hu et al. discloses 1 – 50 cps as a viscosity range suitable for ophthalmic solutions applied to the eye of a subject.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Examiner, Art Unit 1618